HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Helixate FS safely and effectively. See full prescribing information for Helixate FS.

Helixate FS
(Antihemophilic Factor [Recombinant], Formulated with Sucrose)
For Intravenous Use, Lyophilized Powder for Reconstitution
Initial U.S. Approval: 1993

RECENT MAJOR CHANGES

Indications and Usage (1.3) 08/2009

INDICATIONS AND USAGE

Helixate FS is an Antihemophilic Factor (Recombinant) indicated for:

- Control and prevention of bleeding episodes in adults and children (0-16 years) with hemophilia A (1.1).
- Peri-operative management in adults and children with hemophilia A (1.2).
- Routine prophylaxis to reduce the frequency of bleeding episodes and the risk of joint damage in children with hemophilia A with no pre-existing joint damage (1.3).

DOSAGE AND ADMINISTRATION

For intravenous use only (2)

- Each vial of Helixate FS contains the labeled amount of recombinant factor VIII in international units (IU)

Control and prevention of bleeding episodes and peri-operative management (2):

- Dose (units) = body weight (kg) × desired factor VIII rise (IU/dL or % of normal) × 0.5 (IU/kg per IU/dL).
- Frequency of intravenous injection of the reconstituted product is determined by the type of bleeding episode and the recommendation of the treating physician (2.1, 2.2).

For routine prophylaxis in children with no pre-existing joint damage, the recommended dose is 25 IU/kg every other day (2.3).

DOSAGE FORMS AND STRENGTHS

Helixate FS powder is available as 250, 500, 1000, 2000, and 3000 IU in single-use vials (3).

CONTRAINDICATIONS

Do not use in patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components, including mouse or hamster proteins (4).

WARNINGS AND PRECAUTIONS

- Anaphylaxis and severe hypersensitivity reactions are possible. Should symptoms occur, treatment with Helixate FS should be discontinued, and emergency treatment should be sought. Patients may develop hypersensitivity to mouse or hamster protein, which is present in trace amounts in the product (5.2).
- Development of activity-neutralizing antibodies has been detected in patients receiving factor VIII-containing products. If expected plasma factor VIII activity levels are not attained, or if bleeding is not controlled with an expected dose, an assay that measures factor VIII inhibitor concentration should be performed (5.3).

ADVERSE REACTIONS

The most common adverse reactions observed in clinical trials (frequency ≥ 4% of patients) are inhibitor formation in previously untreated and minimally treated patients (PUPs and MTPs), skin-associated hypersensitivity reactions (e.g., rash, pruritus), urticaria, infusion site reactions (e.g., inflammation, pain), and central venous access device (CVAD) line-associated infections.

To report SUSPECTED ADVERSE REACTIONS, contact CSL Behring Pharmacovigilance Department at 1-866-915-6958 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

To report SUSPECTED ADVERSE REACTIONS, contact at or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

USE IN SPECIFIC POPULATIONS

- Pregnancy: No human or animal data. Use only if clearly needed (8.1).
- Pediatric Use: Higher factor VIII clearance has been described in children (4.4-16 years) compared to adults. Dose adjustment may be needed (8.4).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 12/2009

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Control and Prevention of Bleeding Episodes

Helixate® FS is an antihemophilic factor that is indicated for the control and prevention of bleeding episodes in adults and children (0-16 years) with hemophilia A.

1.2 Peri-operative Management

Helixate FS is indicated for surgical prophylaxis in adults and children with hemophilia A.

1.3 Routine Prophylaxis in Children with Hemophilia A with No Pre-existing Joint Damage

Helixate FS is indicated for routine prophylactic treatment to reduce the frequency of bleeding episodes and the risk of joint damage in children with no pre-existing joint damage.
Helixate FS is not indicated for the treatment of von Willebrand's disease.

2 DOSAGE AND ADMINISTRATION

For Intravenous Use After Reconstitution

- Treatment with Helixate FS should be initiated under the supervision of a physician experienced in the treatment of hemophilia A.
- Each vial of Helixate FS has the recombinant factor VIII (rFVIII) potency in international units stated on the label.
- Dosage and duration of treatment depend on the severity of the factor VIII deficiency, the location and extent of bleeding, and the patient's clinical condition.[1] Careful control of replacement therapy is especially important in cases of major surgery or life-threatening bleeding episodes (*see Table 1 and Table 2*).

The expected in vivo peak increase in factor VIII level expressed as IU/dL (or % normal) can be estimated using the following formulas:
Dosage (units) = body weight (kg) × desired factor VIII rise (IU/dL or % or normal) × 0.5 (IU/kg per IU/dL)
OR
IU/dL (or % normal) = Total Dose (IU)/body weight (kg) × 2 [IU/dL]/[IU/kg]
Examples (assuming patient's baseline factor VIII level is <1% of normal):

1. A dose of 1750 IU Helixate FS administered to a 70 kg patient should be expected to result in a peak post-infusion factor VIII increase of 1750 IU × {[2 IU/dL]/[IU/kg]}/[70 kg] = 50 IU/dL (50% of normal).
2. A peak level of 50% is required in a 15 kg child. In this situation, the appropriate dose would be: 50 IU/dL/{[2 IU/dL]/[IU/kg]} × 15 kg = 375 IU.

Doses administered should be titrated to the patient's clinical response. Patients may vary in their pharmacokinetic (e.g., half-life, in vivo recovery) and clinical responses to Helixate FS.[2,3,4] Although the dose can be estimated by the calculations above, it is highly recommended that, whenever possible, appropriate laboratory tests including serial factor VIII activity assays be performed (*see Monitoring Laboratory Tests [5.4] and Pharmacokinetics [12.3]).*

2.1 Control and Prevention of Bleeding Episodes

The careful control of treatment dose is especially important in cases of life–threatening bleeding episodes or major surgery.
The following table can be used to guide dosing in bleeding episodes:
Table 1 Control and Prevention of Bleeding Episodes for Children and Adults

Type of Bleeding Episode	Factor VIII Level Required (IU/dL or % of normal)	Dosage and Frequency Necessary to Maintain the Therapeutic Plasma Level
Minor Early hemarthrosis, minor muscle or oral bleeds.	20-40	10–20 IU per kg Repeat dose if there is evidence of further bleeding.
Moderate Bleeding into muscles, bleeding into the oral cavity, definite hemarthroses, and known trauma.	30-60	15–30 IU per kg Repeat dose every 12–24 hours until bleeding is resolved.
Major Gastrointestinal bleeding. Intracranial, intra-abdominal or intrathoracic bleeding, central nervous system bleeding, bleeding in the retropharyngeal or retroperitoneal spaces, or iliopsoas sheath.	80-100	Initial dose 40–50 IU per kg Repeat dose 20–25 IU per kg every 8–12 hours until bleeding is resolved.

Fractures. Head trauma.		

2.2 Peri-operative Management

The careful control of treatment dose is especially important in cases of major surgery or life-threatening bleeding episodes.
The following table can be used to guide dosing in surgery:
Table 2 Peri-operative Management for Adults and Children

Type of Surgery	Factor VIII Level Required (IU/dL or % of normal)	Dosage and Frequency Necessary to Maintain the Therapeutic Plasma Level
Minor Including tooth extraction.	30-60	15 – 30 IU per kg Repeat dose every 12-24 hours until bleeding is resolved.
Major Examples include tonsillectomy, inguinal herniotomy, synovectomy, total knee replacement, craniotomy, osteosynthesis, and trauma.	100	Pre-operative dose 50 IU per kg Verify 100% activity prior to surgery. Repeat as necessary after 6 to 12 hours initially, and for 10 to 14 days until healing is complete.

2.3 Routine Prophylaxis in Children with No Pre-existing Joint Damage

The recommended dose for routine prophylaxis is 25 IU/kg of body weight every other day.[5]

2.4 Instructions for Use

Helixate FS is administered by intravenous (IV) injection after reconstitution. Patients should follow the specific reconstitution and administration procedures provided by their physicians.
For instructions, patients should follow the recommendations in the FDA-Approved Patient Labeling (*see FDA-Approved Patient Labeling)*.
Reconstitution, product administration, and handling of the administration set and needles must be done with caution. Percutaneous puncture with a needle contaminated with blood can transmit infectious viruses including HIV (AIDS) and hepatitis. Obtain immediate medical attention if injury occurs. Place needles in a sharps container after single use. Discard all equipment, including any reconstituted Helixate FS product, in an appropriate container.

2.5 Preparation and Reconstitution

The procedures below are provided as general guidelines for the reconstitution and administration of Helixate FS. Always work on a clean flat surface and wash hands before performing the following procedures.
1.Warm the unopened diluent and the concentrate to a temperature not to exceed 37°C or 99°F.
2.Place the product vial, diluent vial and Mix2Vial™ on a flat surface.
3.Ensure product and diluent vial flip caps are removed and the stoppers are treated with an aseptic solution and allowed to dry prior to opening the Mix2Vial package.
4.Open the Mix2Vial package by peeling away the lid (Fig. 1).

Figure 1

Leave the Mix2Vial in the clear package. Place the diluent vial on an even surface and hold the vial tight. Grip the Mix2Vial together with the package and snap the blue end onto the diluent stopper (Fig. 2).

Figure 2

5.Carefully remove the clear package from the Mix2Vial set. Make sure that you only pull up the package and not the Mix2Vial set (Fig. 3).

Figure 3

6.With the product vial firmly on a surface, invert the diluent vial with the set attached and snap the transparent adapter onto the product vial stopper (Fig. 4). The diluent will automatically transfer into the product vial.

Figure 4

7.With the diluent and product vial still attached, gently swirl the product vial to ensure the powder is fully dissolved (Fig. 5). Do not shake vial.

Figure 5

8.With one hand grasp the product-side of the Mix2Vial set and with the other hand grasp the blue diluent-side of the Mix2Vial set and unscrew the set into two pieces (Fig. 6)

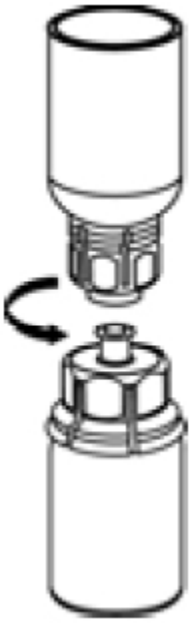

Figure 6

9.Draw air into an empty, sterile syringe. While the product vial is upright, screw the syringe to the Mix2Vial set. Inject air into the product vial. While keeping the syringe plunger pressed, invert the system upside down and draw the concentrate into the syringe by pulling the plunger back slowly (Fig. 7).

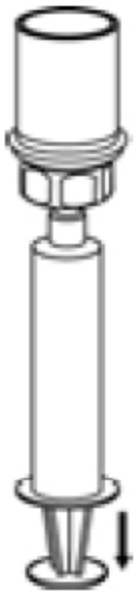

Figure 7

10.Now that the concentrate has been transferred into the syringe, firmly grasp the barrel of the syringe (keeping the syringe plunger facing down) and unscrew the syringe from the Mix2Vial set (Fig. 8). Attach the syringe to an administration set made with microbore tubing. Use of other administration sets without microbore tubing may result in a larger retention of the solution within the administration set.

Figure 8

11.If the same patient is to receive more than one bottle, the contents of two bottles may be drawn into the same syringe through a separate unused Mix2Vial set before attaching the vein needle.
12.Helixate FS should be inspected visually for particulate matter and discoloration prior to administration.

2.6 Administration
For Intravenous Use Only After Reconstitution

- Helixate FS should be inspected visually for particulate matter and discoloration prior to administration. Turbid or discolored solution should be discarded.

- Reconstituted Helixate FS may be stored at room temperature prior to administration, but is to be administered within 3 hours.

- A dose of Helixate FS may be administered over a period of 1 to 15 minutes. The rate of administration however, should be adapted to the response of each individual patient. The pulse rate should be determined before and during administration of Helixate FS. If there is a significant increase in pulse rate, reducing the rate of administration or temporarily halting the injection allows the symptoms to disappear promptly.

3 DOSAGE FORMS AND STRENGTHS

Helixate FS is available as a lyophilized powder in single-use glass vials containing 250, 500, 1000, 2000, and 3000 International Units (IU).

Each vial of Helixate FS is labeled with the recombinant antihemophilic factor activity expressed in IU per vial. This potency assignment employs a factor VIII concentrate standard that is referenced to a WHO International Standard for factor VIII concentrates, and is evaluated by appropriate methodology to ensure accuracy of the results.

4 CONTRAINDICATIONS

Helixate FS is contraindicated in patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components, including mouse or hamster proteins.

5 WARNINGS AND PRECAUTIONS

5.1 General

The clinical response to Helixate FS may vary. If bleeding is not controlled with the recommended dose, the plasma level of factor VIII should be determined and a sufficient dose of Helixate FS should be administered to achieve a satisfactory clinical response. If the patient's plasma factor VIII level fails to increase as expected or if bleeding is not controlled after the expected dose, the presence of an inhibitor (neutralizing antibodies) should be suspected and appropriate testing performed (*see Monitoring Laboratory Tests [5.4])*.

5.2 Anaphylaxis and Severe Hypersensitivity Reactions

Allergic-type hypersensitivity reactions including anaphylaxis have been reported with Helixate FS and have manifested as pruritus, rash, urticaria, hives, facial swelling, dizziness, hypotension, nausea, chest discomfort, cough, dyspnea, wheezing, flushing, discomfort (generalized) and fatigue. Discontinue Helixate FS if symptoms occur and seek immediate emergency treatment.

Helixate FS contains trace amounts of mouse immunoglobulin G (MuIgG) and hamster (BHK) proteins. Patients treated with this product may develop hypersensitivity to these non-human mammalian proteins.

5.3 Neutralizing Antibodies

Patients treated with antihemophilic factor (AHF) products should be carefully monitored for the development of factor VIII inhibitors by appropriate clinical observations and laboratory tests.[6] Inhibitors have been reported following administration of Helixate FS predominantly in previously untreated patients. If expected plasma factor VIII activity levels are not attained, or if bleeding is not controlled with an expected dose, an assay that measures factor VIII inhibitor concentration should be performed *(see Monitoring Laboratory Tests [5.4]).*

5.4 Monitoring Laboratory Tests

- Monitor plasma factor VIII activity levels by the one-stage clotting assay to confirm the adequate factor VIII levels have been achieved and maintained, when clinically indicated (*see Dosage and Administration [2])*.

- Monitor for development of factor VIII inhibitors. If expected factor VIII plasma levels are not attained, or if bleeding is not controlled with the expected dose of Helixate FS, perform assay to determine if factor VIII inhibitor is present. Use Bethesda Units (BU) to titer inhibitors.
- If the inhibitor is less than 10 BU per mL, the administration of additional Helixate FS concentrate may neutralize the inhibitor, and may permit an appropriate hemostatic response.
- Adequate hemostasis may not be achieved if Inhibitor titers are above 10 BU per mL. The inhibitor titer may rise following Helixate FS infusion as a result of an anamnestic response to factor VIII. The treatment or prevention of bleeding in such patients requires the use of alternative therapeutic approaches and agents.

6 ADVERSE REACTIONS

The most serious adverse reactions are systemic hypersensitivity reactions including bronchospastic reactions and/or hypotension and anaphylaxis and the development of high-titer inhibitors necessitating alternative treatments to AHF.

The most common adverse reactions observed in clinical trials (frequency ≥ 4% of patients) are inhibitor formation in previously untreated patients (PUPs) and minimally treated patients (MTPs), skin-related hypersensitivity reactions (e.g., rash, pruritus), infusion site reactions (e.g., inflammation, pain), and central venous access device (CVAD) line-associated infections in patients requiring a CVAD for intravenous administration.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in clinical practice.

Previously Treated Patients (PTPs)

During the clinical studies conducted in PTPs, 451 adverse events (irrespective of the relationship to the study drug) were reported in the course of 24,936 infusions (1.8%). Twenty-four of the 451 adverse events were assessed as related to Helixate FS (0.1%).

Adverse reactions reported by ≥ 4% of the patients are listed in Table 3 below.

Table 3 Adverse Reactions (AR) in Previously Treated Patients (PTPs) with Frequency of ≥ 4%

MedDRA Primary SOC	Preferred Term	Total No. of Patients: 73 No. of Patients with AR (%)	Total No. of Infusions: 24,936 AR per Infusion (%)
Skin and Subcutaneous Tissue Disorders	Rash, pruritus	6 (8.2%)	0.02
General Disorders and Administration Site Conditions	Infusion site reactions	3 (4.1%)	0.01
SOC = System Organ Class			

Previously Untreated Patients (PUPs) and Minimally Treated Patients (MTPs)

In clinical studies with pediatric PUPs and MTPs, 726 adverse events were reported in the course of 9,389 infusions (7.7%). Twenty-nine of the 726 adverse events were assessed as related to Helixate FS (0.3%).

Adverse reactions reported by ≥ 4% of the patients are listed in Table 4 below.

Table 4 Adverse Reactions (AR) in Previously Untreated Patients (PUPs) and Minimally Treated Patients (MTPs) with Frequency of ≥ 4% (Age Range 2-27 months)

MedDRA Primary SOC	Preferred Term	Total No. of Patients: 61 No. of Patients with AR (%)	Total No. of Infusions: 9,389 AR per Infusion (%)
Skin and Subcutaneous Tissue Disorders	Rash, pruritus, urticaria	10 (16.4)	0.01
Blood and Lymphatic System Disorders	Factor VIII inhibition	9 (15)*	N/A
General Disorders and Administration Site Conditions	Infusion site reactions	4 (6.6)	0.04
SOC = System Organ Class			

*****Denominator for *de-novo* inhibitors is N=60, since one patient had a pre-existing inhibitor.

Minimally Treated Patients (MTPs) in the Joint Outcome Study

In the Joint Outcome Study in MTP pediatric patients treated with routine prophylaxis or episodic enhanced treatment for 5.5 years, 46 of the 65 randomized patients experienced adverse events over the study duration. Adverse events were not assessed for their relationship with Helixate FS.

Table 5 Adverse Events (AE) in MTPs in the Joint Outcome Study (Age Range 0-6 years)

MedDRA Primary SOC	Preferred Term	Total No. of Prophylaxis Arm Patients: 32 No. of Patients with AE (%)	Total No. of Enhanced Episodic Arm Patients: 33 No. of Patients with AE (%)
Surgical and Medical Procedures	Central venous catheterization, Catheter removal	19 (59)	18* (55)
Infections and Infestations	Central line infection	6 (19)	6 (18)
General Disorders and Administration Site Conditions	Pyrexia	1 (3)	4 (12)
SOC = System Organ Class			

*****Three patients from the enhanced episodic arm had catheter removal.

Immunogenicity

In clinical studies with 73 PTPs (defined as having more than 100 exposure days), one patient had a pre-existing inhibitor. In the other 72 patients, followed over 4 years, no de-novo inhibitors were observed.

In clinical studies with pediatric PUPs and MTPs, inhibitor development was observed in 9 out of 60 patients (15%), 6 were high titer[1](>5 BU) and 3 were low-titer inhibitors. Inhibitors were detected at a median number of 7 exposure days (range 2 to 16 exposure days).

In the Joint Outcome Study with Helixate FS,[5] de-novo inhibitor development was observed in 8 of 64 patients with negative baseline values (12.5%), 2 patients developed high titer[1] (>5 BU) and were withdrawn from the study. Six patients developed low-titer inhibitors. Inhibitors were detected at a median number of 44 exposure days (range 5 to 151 exposure days).

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post approval use of Helixate FS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Among patients treated with Helixate FS, cases of serious allergic/hypersensitivity reactions (which may include facial swelling, flushing, hives, blood pressure decrease, nausea, rash, restlessness, shortness of breath, tachycardia, tightness of the chest, tingling, urticaria, vomiting) have been reported, particularly in very young patients or patients who have previously reacted to other factor VIII concentrates.

The following table represents the post-marketing adverse reactions as MedDRA Preferred Terms.

Table 6 Post-Marketing Experience

MedDRA Primary SOC	Preferred Term
Blood and Lymphatic System Disorders	FVIII inhibition
Skin and Subcutaneous Tissue Disorders	Pruritus, urticaria, rash
General Disorders and Administration Site Conditions	Infusion site reaction
	Pyrexia
Immune System Disorders	Anaphylactic reaction, other hypersensitivity reactions
SOC = System Organ Class	

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with Helixate FS. It is also not known whether Helixate FS can cause fetal harm when administered to a pregnant woman or affect reproduction capacity. Helixate FS should be used during pregnancy only if clinically needed.

8.2 Labor and Delivery

There is no information available on the effect of factor VIII replacement therapy on labor and delivery. Helixate FS should be used only if clinically needed.

8.3 Nursing Mothers

It is not known whether this drug is excreted into human milk. Because many drugs are excreted into human milk, caution should be exercised if Helixate FS is administered to nursing mothers. Helixate FS should be given to nursing mothers only if clinically needed.

8.4 Pediatric Use

Safety and efficacy studies have been performed in previously untreated and minimally treated pediatric patients. Children in comparison to adults present higher factor VIII clearance values and thus lower recovery of factor VIII. This may be explained by differences in body composition[7] and should be taken into account when dosing or following factor VIII levels in such a population (*see Pharmacokinetics [12.3])*. Routine prophylactic treatment in children ages 0-2.5 years with no pre-existing joint damage has been shown to reduce spontaneous joint bleeding and the risk of joint damage. This data can be extrapolated to ages >2.5-16 years for children who have no existing joint damage (*see Clinical Studies [14])*.

8.5 Geriatric Use

Clinical studies with Helixate FS did not include patients aged 65 and over. Dose selection for an elderly patient should be individualized.

11 DESCRIPTION

Helixate FS Antihemophilic Factor (Recombinant) is a coagulation factor VIII produced by recombinant DNA technology. It is produced by Baby Hamster Kidney (BHK) cells into which the human factor VIII gene has been introduced.[8] The cell culture medium contains Human Plasma Protein Solution (HPPS) and recombinant insulin, but does not contain any proteins derived from animal sources. Helixate FS is a purified glycoprotein consisting of multiple peptides including an 80 kD and various extensions of the 90 kD subunit. It has the same biological activity as factor VIII derived from human plasma. No human or animal proteins, such as albumin, are added during the purification and formulation processes of Helixate FS.

The purification process includes a solvent/detergent virus inactivation step in addition to the use of the purification methods of ion exchange chromatography, monoclonal antibody immunoaffinity chromatography, along with other chromatographic steps designed to purify recombinant factor VIII and remove contaminating substances.
Additionally, the manufacturing process was investigated for its capacity to decrease the infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), considered as a model for the vCJD and CJD agents.[9-21] Several of the individual production and raw material preparation steps in the Helixate FS manufacturing process have been shown to decrease TSE infectivity of that experimental model agent. TSE reduction steps include the Fraction II+III separation step for HPPS (6.0 $\log_{10}$) and an anion exchange chromatography step (3.6 $\log_{10}$).
Helixate FS is formulated with the following as stabilizers *(see Table 7)* in the final container and is then lyophilized. The final product is a sterile, nonpyrogenic, preservative-free, powder preparation for intravenous (IV) injection. Intravenous administration of sucrose contained in Helixate FS will not affect blood glucose levels.
Table 7 Stabilizers Contained in Helixate FS Final Container

Stabilizer	250 IU, 500 IU, 1000 IU	2000 IU, 3000 IU
Sucrose	0.9 – 1.3%	0.9 – 1.2%
Glycine	21 – 25 mg/mL	20 – 24 mg/mL
Histidine	18 – 23 mmol/L	17 – 22 mmol/L

The following inactive ingredients/excipients are also contained in the final product:
Table 8 Inactive Ingredients/Excipients

Inactive Ingredient/Excipient	250 IU, 500 IU, 1000 IU	2000 IU, 3000 IU
Sodium	27 – 36 mEq/L	26 – 34 mEq/L
Calcium	2.0 – 3.0 mmol/L	1.9 – 2.9 mmol/L
Chloride	32 – 40 mEq/L	31 – 38 mEq/L
Polysorbate 80	64 – 96 μg/mL	64 – 96 μg/mL
Sucrose	28 mg/vial	52 mg/vial
Imidazole, tri-n-butyl phosphate, and copper	Trace amounts	Trace amounts

Each vial of Helixate FS contains the labeled amount of recombinant factor VIII in international units (IU). One IU, as defined by the World Health Organization standard for blood coagulation factor VIII, human, is approximately equal to the level of factor VIII activity found in 1 mL of fresh pooled human plasma.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Helixate FS temporarily replaces the missing clotting factor VIII that is needed for effective hemostasis.

12.2 Pharmacodynamics
The aPTT is prolonged in patients with hemophilia. Determination of activated partial thromboplastin time (aPTT) is a conventional in vitro assay for biological activity of factor VIII. Treatment with Helixate FS normalizes the aPTT over the effective dosing period.

12.3 Pharmacokinetics
The pharmacokinetic properties of Helixate FS were investigated in two separate studies in previously treated patients, adults and children.
Pharmacokinetic studies with Helixate FS were conducted in 20 PTPs (ages 12 to 33 years) with severe hemophilia A in North America. The pharmacokinetic parameters for Helixate FS were measured in a randomized, crossover clinical trial with the predecessor HELIXATE product with a single dose administration of 50 IU/kg. After 24 weeks, the same dose of Helixate FS was administered to the same patients. The recovery and half-life data for Helixate FS were unchanged after 24 weeks of continued treatment with sustained efficacy and no evidence of factor VIII inhibition *(see Table 9)*.
Table 9 Pharmacokinetic Parameters for Helixate FS Compared to HELIXATE

Parameter	Helixate FS		HELIXATE
	Initial PK Mean (±SD)	PK at week 24 Mean (±SD)	Reference Mean (±SD)
AUC (IU · h/dL)	1588.05 ± 344.32	1487.08 ± 381.73	1879.02 ± 412.32
Cmax (IU/dL)	114.95 ± 20.19	109.42 ± 20.09	127.40 ± 33.21
Half-life (hr)	13.74 ± 1.82	14.60 ± 4.38	14.07 ± 2.62
In Vivo Recovery (IU/dL / IU/kg)	2.20 ± 0.34	2.11 ± 0.37	2.43 ± 0.60

The pharmacokinetics of Helixate FS were investigated in pediatric PTPs (4.4-18.1 years of age, average age 12).[7] The pharmacokinetic parameters in children compared to adults show differences in higher clearance, lower incremental in vivo factor VIII recovery and a shorter factor VIII half-life. This might be explained by differences in body composition such as body surface area and plasma volume. The pharmacokinetic parameters are depicted in Table 10.

Table 10 Pharmacokinetic Parameters for Helixate FS in Children

Parameter	Mean (range)
AUC (IU · h/dL)	1320.0
Clearance (mL/h·kg)	4.1
Half-life (hr)	10.7 (7.8 – 15.3)
In Vivo Recovery (IU/dL / IU/kg)	1.9 (1.25 – 2.76)

13 NONCLINICAL TOXICOLOGY

Preclinical studies evaluating Helixate FS in hemophilia A with mice, rats, rabbits, and dogs demonstrated safe and effective restoration of hemostasis. Doses several fold higher than the recommended clinical dose (related to body weight) did not demonstrate any acute or subacute toxic effect for Helixate FS in laboratory animals.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted with Helixate FS to assess its mutagenic or carcinogenic potential and impairment of fertility. Helixate FS has been shown to be comparable to the predecessor product with respect to its biochemical and physiochemical properties, as well as its non-clinical in vivo pharmacology and toxicology. By inference, the predecessor product and Helixate FS would be expected to have equivalent mutagenic and carcinogenic potential.

The predecessor product did not demonstrate reverse mutation or chromosomal aberrations at doses substantially greater than the maximum expected clinical dose. In vivo evaluation with the predecessor product in animals using doses ranging between 10 and 40 times the expected clinical maximum also indicated that the predecessor product did not possess a mutagenic potential. Long-term investigations of carcinogenic potential in animals have not been performed due to the immune response to heterologous proteins in all non-human mammalian species.

14 CLINICAL STUDIES

14.1 Previously Treated Patients (PTPs)

A total of 73 patients with severe (≤ 2% FVIII) hemophilia A, ages 12–59, who had been previously treated with other recombinant or with plasma-derived AHF products, were treated up to 54-months in open label studies with Helixate FS in Europe and North America. A total of 5,684 bleeding episodes were treated during the studies. Patients could be treated on demand or on prophylaxis. Regularly scheduled prophylaxis treatment represented 76% of all infusions (treatment regimens of 2-3 infusions per week) *(see Table 11)*.

Table 11 Previously Treated Patients (PTPs) Clinical Trial Results

Clinical Parameters	Results
No. of Infusions of Helixate FS Administered	24,924
No. of IU Administered	45 million IU
No. of Bleeds Treated with Helixate FS	5,684
Percentage of Bleeds Treated with One or Two Infusions of Helixate FS	one infusion: 79.7% two infusions: 13.0% total: 92.7%
Mean Helixate FS Dose per Treatment Infusion (in Europe and North America, Respectively)	Approximately 32.5 and 29.6 IU/kg per treatment infusion

A total of 31 patients received Helixate FS for 43 surgical procedures during the PTP studies. There were both minor and major surgery types, 27 and 16 respectively. The surgeon or treating physician assigned a rating to the hemostatic outcome according to 4 categories; "excellent", "good", "moderate", or "none". Hemostasis was rated as satisfactory ("excellent" or "good") in all cases *(see Table 13)*.

14.2 Previously Untreated and Minimally Treated Patients (PUPs and MTPs)

Helixate FS has been used in the treatment of bleeding episodes in previously untreated pediatric patients (PUPs) and minimally treated patients (MTPs) with severe (< 2% FVIII) hemophilia A. There were 37 PUPs and 24 MTPs (defined as having equal to or less than 4 exposure days) treated with a total of 9,419 infusions of Helixate FS for a follow up duration up to 3.1 years. A total of 1,047 bleeding episodes were treated.

Table 12 Previously Untreated and Minimally Treated Patients (PUPs and MTPs) Clinical Trial Results

Clinical Parameters	Results
No. of Infusions of Helixate FS Administered	9,419
No. of Exposure Days to Helixate FS (median)	115 exposure days
No. of IU Administered	7.5 million IU
No. of Bleeds Treated with Helixate FS	1,047
Percentage of Bleeds Treated with One or Two Infusions of Helixate FS	one infusion: 73.1% two infusions: 15.0% total: 88.1%

A total of 29 surgical procedures were performed in 23 patients during the PUPs and MTPs study. There were both minor and major surgery types, 23 and 6 respectively. The surgeon or treating physician assigned a rating to the hemostatic outcome according to 4 categories; "excellent", "good", "moderate", or "none". Hemostasis was rated as satisfactory ("excellent" or "good") in all cases *(see Table 13)*.

Table 13 Surgical Procedures Performed During PTPs and PUPs/MTPs Clinical Trials

Type of Surgery	PTPs (N=31)		PUPs/MTPs (N=23)	
	No. of Surgical Events	Outcome "Good" or "Excellent"	No. of Surgical Events	Outcome "Good" or "Excellent"
Minor Surgery (i.e. tooth extractions, catheter implantations, liver biopsies)	24	100%	21	100%
Major Surgery (i.e. joint replacements, craniotomies, gastrointestinal resection)	16	100%	6	100%
Total	43		29	

14.3 Pediatric Prophylaxis and Joint Damage Risk Reduction

A total of 65 boys less than 30 months of age with severe hemophilia A (FVIII level ≤ 2 IU/dL) and with ≤ 2 bleeds into each index joint and normal baseline joint imaging, were observed for up to 5.5 years in a multicenter, open-label, prospective, randomized, controlled clinical study.[5] Patients received either 25 IU/kg every other day (primary prophylaxis; n=32) or at least 3 doses totaling a minimum of 80 IU/kg at the time of a bleeding episode (enhanced episodic; n=33). Joint damage was evaluated by magnetic resonance imaging (MRI) or radiography, as well as the frequency of bleeding episodes. Joint damage detected by MRI or radiography in the ankles, knees, and elbows (i.e. index joints) was statistically significantly lower (p=0.002) for subjects receiving prophylactic therapy (7%) than for subjects receiving episodic therapy (42%). This corresponds to a 6.29-fold relative risk of joint damage for subjects treated with enhanced episodic therapy compared to prophylaxis. The mean rate of index joint hemorrhages for subjects on episodic therapy was 4.89 bleeds per year, versus 0.63 bleeds per year observed in the prophylaxis arm. Three of 33 (9.1%) subjects in the episodic arm experienced recurrent life threatening bleeds (intracranial, gastrointestinal) compared to no subjects in the prophylaxis arm. On a per joint basis, joints in the regular prophylaxis arm were 8-fold more likely to remain damage-free than those in the episodic arm. Joint damage was most frequently observed in ankle joints and was detected at higher rates by MRI than by radiography. Ankles were also the index joint that demonstrated the highest frequency of bleeding events in this study (left ankle, mean 2.7 hemorrhages; right ankle, mean 2.6 hemorrhages).

As shown in Table 14 below, the incidence of joint damage was statistically significantly lower in the prophylactic group as compared to the episodic treatment group when assessed by MRI, or either MRI or radiography, using predefined criteria (described below) for establishing joint damage. However, there was no statistically significant difference between the two groups when joint damage was assessed by radiography alone.

To evaluate joint damage, MRIs were scored using a scale developed by Nuss et al.[22], and X-rays were scored using the method of Pettersson et al.[23] Both scales have been validated in various clinical trials and are routinely used for joint damage evaluation in hemophiliacs. Joint damage was defined as bone and/or cartilage damage including subchondral cysts, erosions and cartilage loss with narrowing of joint space. This corresponded to a total MRI score of ≥ 7 or an X-ray score of ≥ 1 in any of the following categories: subchondral cysts, erosions of joint surfaces or narrowing of joint spaces. Images were read separately by two independent radiologists centrally. Any discrepant reading was read by an independent third radiologist who was not aware of the initial reading results. The concordant reading of two out of three readers was used for analysis purposes.

Table 14 Subjects with Joint Damage (Subjects with Available Baseline and Endpoint Data)

Endpoint Assessment	Prophylaxis		Episodic Therapy		p-value
	Incidence (%)	Relative Risk (95% CI)	Incidence (%)	Relative Risk (95% CI)	
MRI	2/27 (7%)	0.17 (0.04, 0.67)	13/29 (45%)	6.05 (1.50, 24.38)	0.002
Radiography	1/28 (4%)	0.19 (0.02, 1.55)	5/27 (19%)	5.19 (0.65, 41.54)	0.101
MRI or Radiography	2/30 (7%)	0.16 (0.04, 0.65)	13/31 (42%)	6.29 (1.55, 25.55)	0.002

Relative Risk is the risk of damage to one or more index joints on the given therapy as compared to the other therapy.
P-value is from the 2-sided Fisher Exact Test comparing the incidence of joint damage between treatment groups.

As shown in Table 15 below, the assessment of endpoints in all randomized subjects assuming that those without complete baseline and endpoint data are treatment failures (intention-to-treat analysis). The incidence of joint damage was statistically significantly lower in the prophylactic group as compared to the episodic treatment group, with similar p-values, when assessed by MRI, or either MRI or radiography.

Table 15 Subjects with Joint Damage (All Randomized Subjects Assuming Subjects without Complete Baseline and Endpoint Data as Treatment Failures)

Endpoint Assessment	Prophylaxis (n=32)		Episodic Therapy (n=33)		p-value
	Incidence (%)	Relative Risk (95% CI)	Incidence (%)	Relative Risk (95% CI)	
MRI	7 (22%)	0.42 (0.20, 0.88)	17 (52%)	2.35 (1.13, 4.90)	0.020
Radiography	5 (16%)	0.47 (0.18, 1.20)	11 (33%)	2.13 (0.83, 5.45)	0.150
MRI or Radiography	8 (25%)	0.43 (0.22, 0.85)	19 (58%)	2.30 (1.18, 4.49)	0.012

Relative Risk is the risk of damage to one or more index joints on the given therapy as compared to the other therapy.
P-value is from the 2-sided Fisher Exact Test comparing the incidence of joint damage between treatment groups.

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16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Helixate FS is available as a kit in the following single-use glass vial sizes. A suitable volume of Sterile Water for Injection, USP and Mix2Vial™ filter transfer device *(see Preparation and Reconstitution [2.5])* are provided in the kit.

NDC Number	Approximate FVIII Activity (IU)	Diluent (mL)
0053-8131-02	250	2.5
0053-8132-02	500	2.5
0053-8133-02	1000	2.5
0053-8134-02	2000	5.0
0053-8135-02	3000	5.0

Actual factor VIII activity in IU is stated on the label of each Helixate FS vial.

16.2 Storage and Handling

Product as Packaged for Sale:

- Store Helixate FS under refrigeration (2–8°C or 36–46°F).
- Storage of lyophilized powder at room temperature (up to 25°C or 77°F) for 3 months, such as in home treatment situations, may be done. If Helixate FS is stored outside the refrigerator, please add the date removed from refrigeration and note a new expiry date on the carton and vial. The new expiry date should be 3 months from the date product is removed from the refrigerator, or the previously stamped expiry date, whichever is shorter.
- Do not return to the refrigerator once Helixate FS is removed from refrigeration.
- Do not use Helixate FS after the expiration date indicated on the vial.
- Do not freeze.

• Protect from extreme exposure to light and store the lyophilized powder in the carton prior to use.

Product After Reconstitution:

• Administer Helixate FS within 3 hours after reconstitution.

• It is recommended to use the administration set provided.

17 PATIENT COUNSELING INFORMATION

See Patient Product Information (PPI) and Instructions for Use.

Advise patients to report any adverse reactions or problems following Helixate FS administration to their physician or healthcare provider.

• Allergic-type hypersensitivity reactions have been reported with Helixate FS. Warn patients of the early signs of hypersensitivity reactions [including hives (rash with itching), generalized urticaria, tightness of the chest, wheezing, hypotension] and anaphylaxis. Advise patients to discontinue use of the product if these symptoms occur and seek immediate emergency treatment with resuscitative measures such as the administration of epinephrine and oxygen.

• In clinical studies with Helixate FS, a 15% incidence of inhibitor development was observed in PUPs/MTPs and zero de-novo inhibitors were observed with the PTPs. Inhibitor formation may occur at any time in the treatment of a patient with hemophilia A. Advise patients to contact their physician or treatment center for further treatment and/or assessment, if they experience a lack of clinical response to factor VIII replacement therapy, as this may be a manifestation of an inhibitor.

• Advise patients to consult with their healthcare provider prior to travel. While traveling advise patients to bring an adequate supply of Helixate FS based on their current regimen of treatment.

FDA-APPROVED PATIENT LABELING - PATIENT PRODUCT INFORMATION (PPI)

Helixate FS (he-liks-#t)

Antihemophilic Factor (Recombinant)

Formulated with Sucrose

This leaflet summarizes important information about Helixate FS. Please read it carefully before using this medicine. This information does not take the place of talking with your healthcare provider, and it does not include all of the important information about Helixate FS. If you have any questions after reading this, ask your healthcare provider.

Do not attempt to self-infuse unless you have been taught how by your healthcare provider or hemophilia center.

What is Helixate FS?

Helixate FS is a medicine used to replace clotting factor (factor VIII or antihemophilic factor) that is missing in people with hemophilia A (also called "classic" hemophilia). Hemophilia A is an inherited bleeding disorder that prevents blood from clotting normally.

Helixate FS is used to prevent and control bleeding in adults and children (0-16 years) with hemophilia A. Your healthcare provider may give you Helixate FS when you have surgery. Helixate FS can reduce the number of bleeding episodes when used regularly and reduce the risk of joint damage in children.

Helixate FS is not used to treat von Willebrand's Disease.

Who should not use Helixate FS?

You should not use Helixate FS if you

• are allergic to rodents (like mice and hamsters).

• are allergic to any ingredients in Helixate FS.

Tell your healthcare provider if you are pregnant or breast-feeding because Helixate FS may not be right for you.

What should I tell my healthcare provider before I use Helixate FS?

Tell your healthcare provider about all of your medical conditions.

Tell your healthcare provider and pharmacist about all of the medicines you take, including all prescription and nonprescription medicines, such as over-the-counter medicines, supplements, or herbal remedies.

Tell your healthcare provider if you have been told that you have inhibitors to factor VIII (because Helixate FS may not work for you).

What are the possible side effects of Helixate FS?

You could have an allergic reaction to Helixate FS. Call your healthcare provider right away and stop treatment if you get

• rash or hives

• itching

• tightness of the chest or throat

• difficulty breathing

• light-headed, dizziness

• nausea

• decrease in blood pressure

Your body can also make antibodies, called "inhibitors", against Helixate FS, which may stop Helixate FS from working properly. Consult with your healthcare provider to make sure you are carefully monitored with blood tests for the development of inhibitors to factor VIII.
Other common side effects of Helixate FS are
• Local injection site reactions (pain, swelling, irritation at infusion site)

• Infections from implanted injection device

Tell your healthcare provider about any side effect that bothers you or does not go away.
Finding veins for injections may be difficult in young children. When frequent injections are required your child's healthcare provider may propose to have a device surgically placed under the skin to facilitate access to the bloodstream. These devices may result in infections.
These are not all the possible side effects with Helixate FS.
You can ask your healthcare provider for information that is written for healthcare professionals.

How do I store Helixate FS?

Do not freeze Helixate FS.
Helixate FS vials containing powdered product (without sterile diluent added) should be stored in a refrigerator (2°C–8°C [36°F–46°F]), or at room temperature (up to 25°C or 77°F) for up to 3 months.
If you choose to store Helixate FS at room temperature, be sure to note on the carton the date that the product is removed from refrigeration. Store vials in their original carton and protect them from extreme exposure to light.
Reconstituted product (after mixing dry products with wet diluent) must be used within 3 hours and cannot be stored.
Throw away any unused Helixate FS after the expiration date.
Do not use reconstituted Helixate FS if it is not clear to slightly cloudy and colorless.

What else should I know about Helixate FS and hemophilia A?

Medicines are sometimes prescribed for purposes other than those listed here. Do not use Helixate FS for a condition for which it is not prescribed. Do not share Helixate FS with other people, even if they have the same symptoms that you have.
This leaflet summarizes the most important information about Helixate FS. If you would like more information, talk to your healthcare provider. You can ask your healthcare provider or pharmacist for information about Helixate FS that was written for healthcare professionals.

Instructions for use

How should I take Helixate FS?

Do not attempt to self-infuse unless you have been taught how by your healthcare provider or hemophilia center.

See the step-by-step instructions for reconstituting Helixate FS at the end of this leaflet and the Mix2Vial™ filter transfer device instruction leaflet provided.
You should always follow the specific instructions given by your healthcare provider. The steps listed below are general guidelines for using Helixate FS. If you are unsure of the procedures, please call your healthcare provider before using.
Call your healthcare provider right away if bleeding is not controlled after using Helixate FS.
Your healthcare provider will prescribe the dose that you should take.
Your healthcare provider may need to take blood tests from time to time.
Talk to your healthcare provider before traveling. You should plan to bring enough Helixate FS for your treatment during this time.
Carefully handle Helixate FS. Dispose of all materials, including any leftover reconstituted Helixate FS product, in an appropriate container.

Reconstitution and use of Helixate FS

Always work on a clean flat surface and wash your hands before performing the following procedures:
1. Warm the unopened diluent and the concentrate to a temperature not to exceed 37°C or 99°F.
2. Place the product vial, diluent vial and Mix2Vial™ on a flat surface.
3. Ensure product and diluent vial flip caps are removed and the stoppers are treated with an aseptic solution and allowed to dry prior to opening the Mix2Vial package.
4. Open the Mix2Vial package by peeling away the lid (Fig. 1).

Figure 1

Leave the Mix2Vial in the clear package. Place the diluent vial on an even surface and hold the vial tight. Grip the Mix2Vial together with the package and snap the blue end onto the diluent stopper (Fig. 2).

Figure 2

5. Carefully remove the clear package from the Mix2Vial set. Make sure that you only pull up the package and not the Mix2Vial set (Fig. 3).

Figure 3

6. With the product vial firmly on a surface, invert the diluent vial with the set attached and snap the transparent adapter onto the product vial stopper (Fig. 4). The diluent will automatically transfer into the product vial.

Figure 4

7. With the diluent and product vial still attached, gently swirl the product vial to ensure the powder is fully dissolved (Fig. 5). Do not shake vial.

Figure 5

8. With one hand grasp the product-side of the Mix2Vial set and with the other hand grasp the blue diluent-side of the Mix2Vial set and unscrew the set into two pieces (Fig. 6).

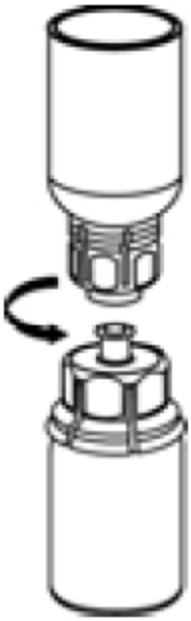


Figure 6

9. Draw air into an empty, sterile syringe. While the product vial is upright, screw the syringe to the Mix2Vial set. Inject air into the product vial. While keeping the syringe plunger pressed, invert the system upside down and draw the concentrate into the syringe by pulling the plunger back slowly (Fig. 7).

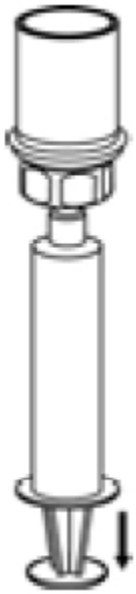


Figure 7

10. Now that the concentrate has been transferred into the syringe, firmly grasp the barrel of the syringe (keeping the syringe plunger facing down) and unscrew the syringe from the Mix2Vial set (Fig. 8). Attach the syringe to an administration set made with microbore tubing. Use of other administration sets without microbore tubing may result in a larger retention of the solution within the administration set.

Figure 8

11. If the same patient is to receive more than one bottle, the contents of two bottles may be drawn into the same syringe through a separate unused Mix2Vial set before attaching the vein needle.
12. Helixate FS should be inspected visually for particulate matter and discoloration prior to administration.

Rate of administration

The entire dose of Helixate FS can usually be infused within 1 to 15 minutes. However, your healthcare provider will determine the rate of administration that is best for you.

Resources at CSL Behring available to the patient:

For Adverse Reaction Reporting contact:
CSL Behring Pharmacovigilance Department at 1-866-915-6958

Contact CSL Behring to receive more product information:

Consumer Affairs 1-888-508-6978
Customer Support 1-800-683-1288
Reimbursement Services 1-800-676-4266

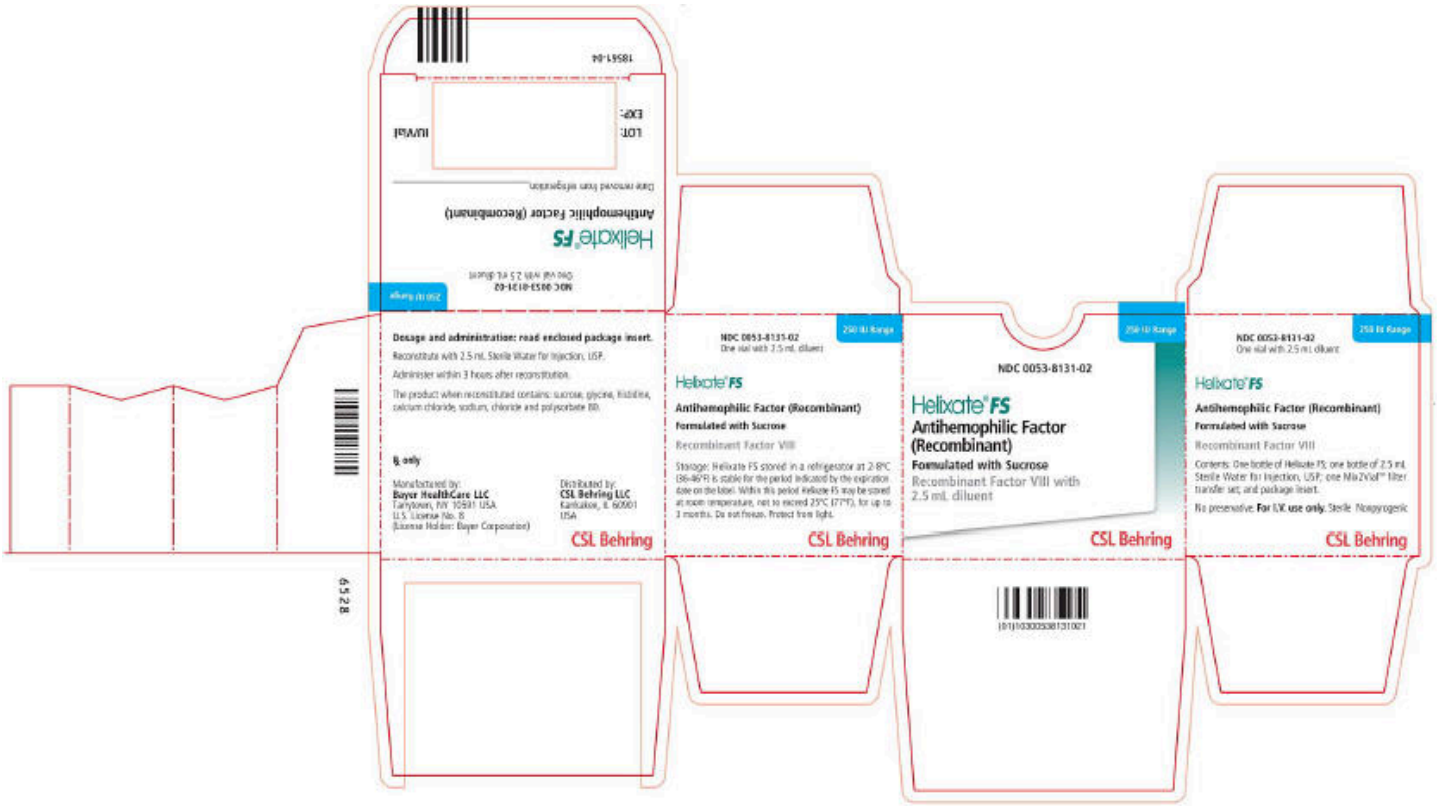
For more information, visit www.HelixateFS.com

Manufactured by:
Bayer HealthCare LLC Tarrytown, NY 10591 USA
U.S. License No. 8 (License Holder: Bayer Corporation)
Distributed by:
CSL Behring LLC Kankakee, IL 60901 USA
Revised: August 2009

Mix2Vial™ is a trademark of West Pharmaceutical Services, Inc. in the United States.

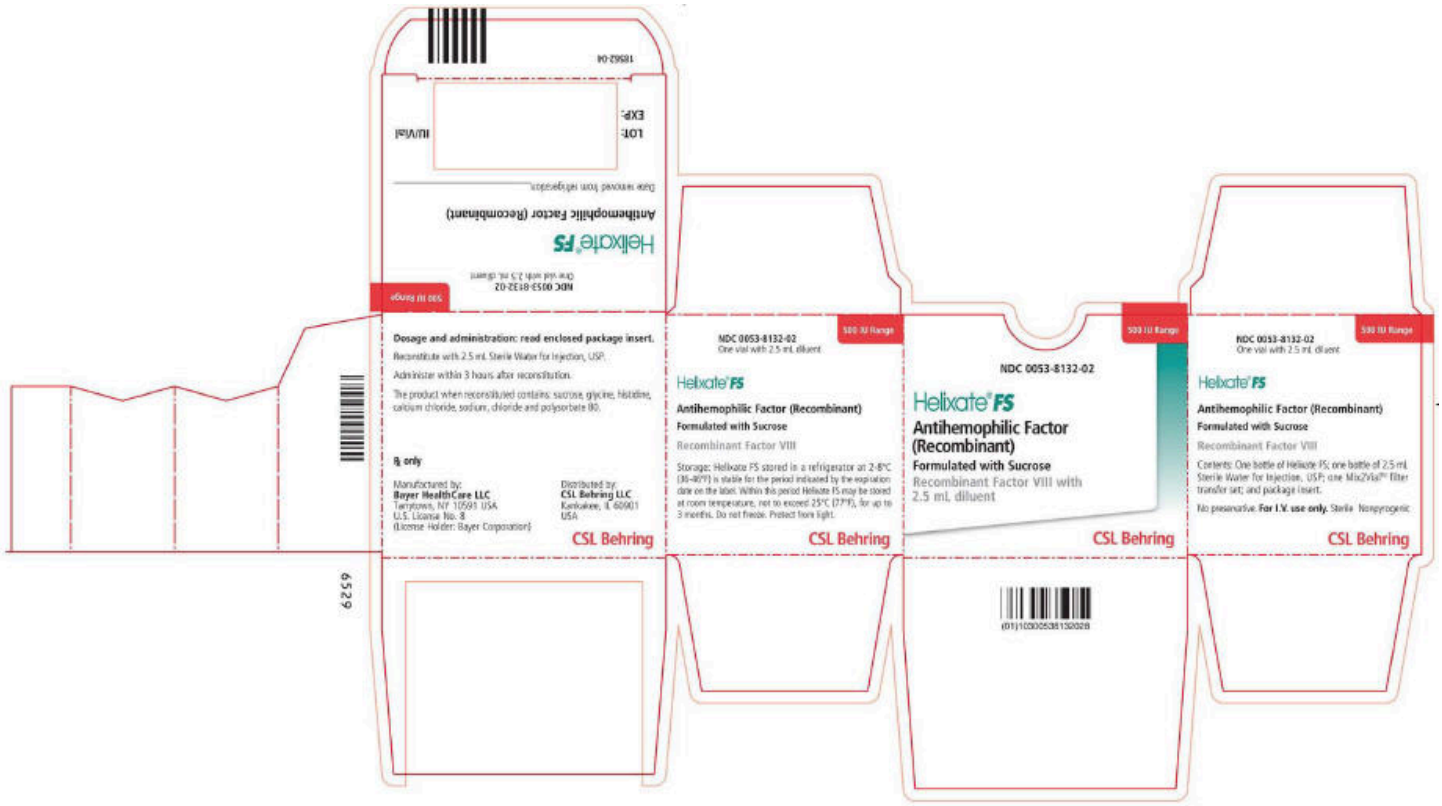
PRINCIPAL DISPLAY PANEL - 250 IU Range
250 IU Range
NDC 0053-8131-02

Helixate®***FS***
Antihemophilic Factor
(Recombinant)
Formulated with Sucrose
Recombinant Factor VIII with
2.5 mL diluent
CSL Behring



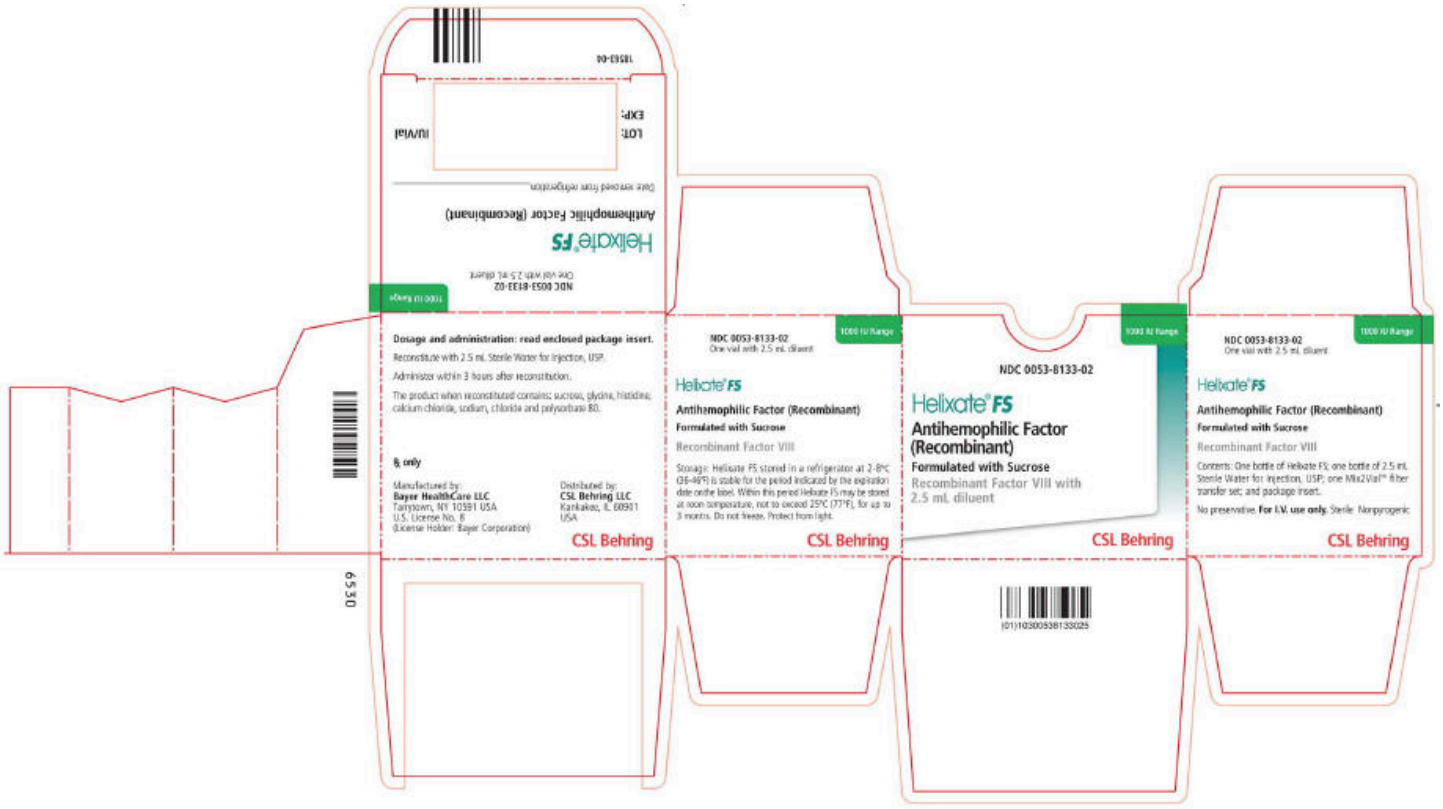
PRINCIPAL DISPLAY PANEL - 500 IU Range
500 IU Range
NDC 0053-8132-02

Helixate®***FS***
Antihemophilic Factor
(Recombinant)
Formulated with Sucrose
Recombinant Factor VIII with
2.5 mL diluent
CSL Behring



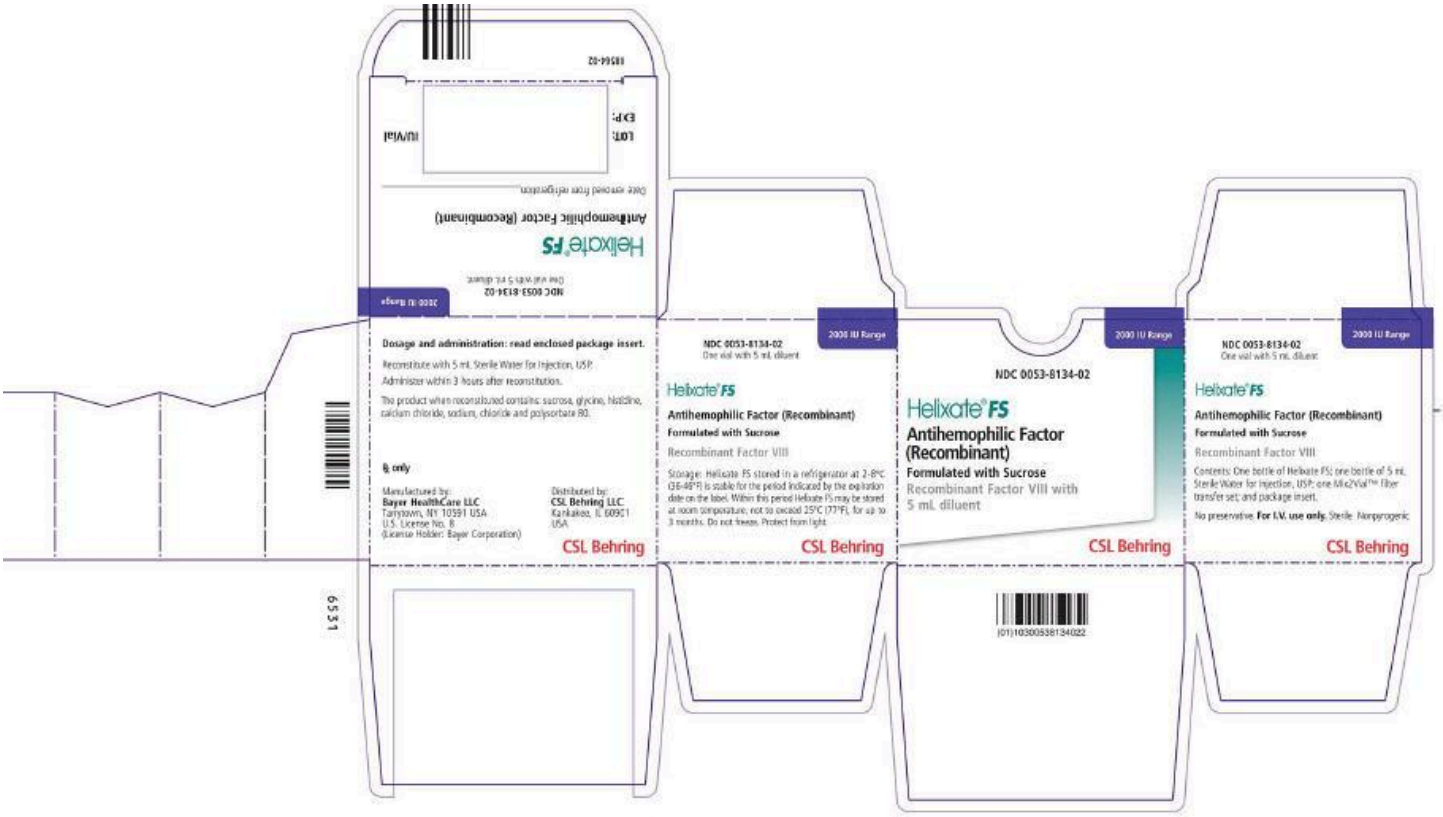
PRINCIPAL DISPLAY PANEL - 1000 IU Range
1000 IU Range
NDC 0053-8133-02

Helixate®***FS***
Antihemophilic Factor
(Recombinant)
Formulated with Sucrose
Recombinant Factor VIII with
2.5 mL diluent
CSL Behring



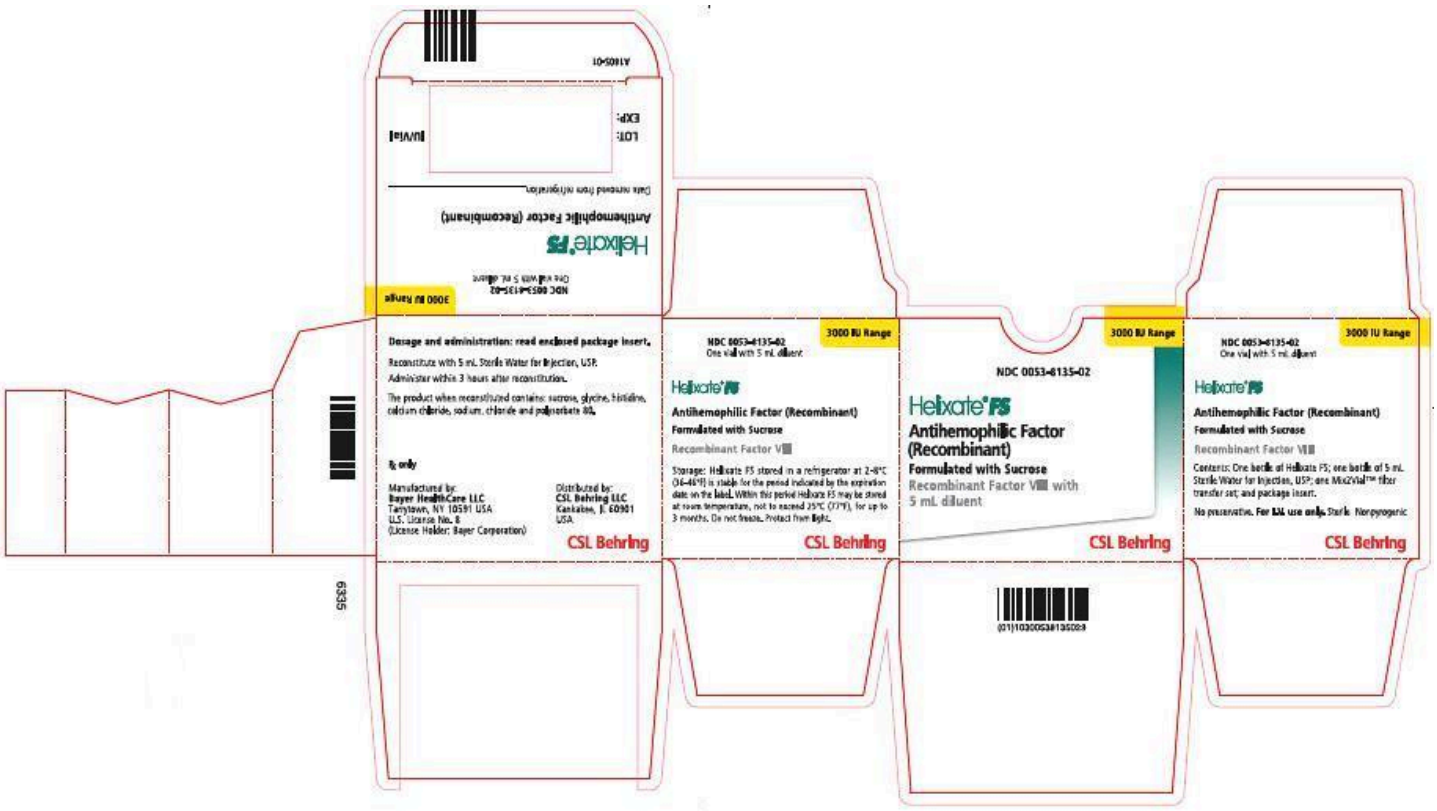
PRINCIPAL DISPLAY PANEL - 2000 IU Range
2000 IU Range
NDC 0053-8134-02

Helixate®***FS***
Antihemophilic Factor
(Recombinant)
Formulated with Sucrose
Recombinant Factor VIII with
5 mL diluent
CSL Behring



PRINCIPAL DISPLAY PANEL - 3000 IU Range
3000 IU Range
NDC 0053-8135-02

Helixate®***FS***
Antihemophilic Factor
(Recombinant)
Formulated with Sucrose
Recombinant Factor VIII with
5 mL diluent
CSL Behring



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